REMARKS

Claims 1, 3-8, 16-25 and 28-45 and 48-50 remain in this application. Claims 26-27 are cancelled. Claims 18, 19 and 21 have been withdrawn as the result of being drawn to a non-elected species (and subject to rejoinder), while claims 28-45 and 48-50 have been withdrawn as a result of an earlier restriction. Claim 8 has been amended to correct for a typographical error.

Support for the amendment appears at least as indicated below:

- Claim 1: page 2, line 33 to page 3, line 1. Page 3, line 11.
- Claim 8: page 3, lines 3-4.

In view of the Examiner's earlier restriction, applicants retain the right to present the subject matter of withdrawn and cancelled claims in subsequent prosecution.

The Rejection under 35 U.S.C. § 112, Second Paragraph.

Claims 2-6 and 10-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, the Examiner has asserted that the term "protein" recited in claims 2-6and 10-14 has insufficient antecedent basis.

In response, Applicants' amendments renders the rejection moot.

The Rejection under 35 U.S.C. § 102(e) over Kaisheva *et al.*, (US2003/0138417).

Claims 1-15 and 20 are rejected under 35 U.S.C. § 102(e) as being anticipated by US2003/0138417 (" '417"). Specifically, the Examiner alleges that the '417 disclosure teaches a stable liquid antibody in a concentration of 100 mg/ml or more, in 30-70 mM histidine buffer at pH 5.5-5.7, with 75-200 mM tonicity modifier (*e.g.*, arginine) and 0.01% polysorbate.

In response, Applicants' amendments respectfully render the Examiner's rejection moot.

It is axiomatic that anticipation under 35 US.C. § 102 requires the disclosure of each and every element of the claimed invention. *W.L. Gore and Associates, Inc. v. Garlock, Inc.* 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851. Moreover, the disclosure of such a reference must be "enabling", in that it must place the invention in the possession of the public without the exertion of another's own inventive skill. *In re Brown*, 141 USPQ 245, 249 (CCPA 1964). Under MPEP § 2131.03 II., when a prior art reference discloses a range that overlaps with the claimed range, anticipation requires that the claimed range be disclosed in the reference with "sufficient specificity." *Ex Parte Lee*, 31 USPQ2d 1105 (Bd Pat. App. & Inter. 1993). The determination of what constitutes "sufficient specificity" is a fact-dependent question, in which especially favorable facts for a finding of patentability exist when the prior art discloses a broad range and the claimed range is narrow and there is evidence of unexpected results in the narrow range.

In re Brown was a decision of the Court of Customs and Patent Appeals reversing the Board of Patent Appeals confirmation of an Examiner rejection of anticipation under 35 U.S.C. § 102. In *Brown*, Applicants claims were generic to perfluoro siloxane homopolymers, while the prior art described copolymers of perfluoroaklylsiloxane, along with a statement that "attempts to prepare fluorine-containing silicone homopolymers have been unsuccessful." The Examiner referred to the unsuccessful attempts at creating the homopolymers sufficient to "constitute a conception of the broad idea of homopolymers." Faulting the Board's (and the Examiner's analysis), the Court held that the test is not simply the mere "printed conception" or "printed contemplation", but rather must be sufficient to show possession of the public. In other words a description that is "so particular and definite that from it alone, without experiment or the exertion of . . . inventive skill, any person versed in the art to which it appertains could construct and use it." *Brown* at 249.

Applying the above recitations of the law of anticipation to the outstanding rejection, it should be first noted that '417 discloses L-arginine in a long laundry list of possible amino acid excipients [paragraph 52], while the present invention describes specifically and uniquely the use

of arginine hydrochloride. The Examples of the '417 does not suggest the combination of any other salt in combination with arginine. Second, the highest concentration of specifically-described liquid antibody formulations in '417 is 100 mg/ml, including; (1) Daclizumab (anti-IL-2R Ab) - Examples 1-7; (2) HAIL-12 (anti-IL12) - Examples 8-9; and (3) HuEP5C7 (anti-L selectin) - Example 11. Thus, despite the text recitation of 100 mg/ml **or greater** [paragraph 54], there is no specific disclosure of an antibody formulation having a final concentration greater than 100 mg/ml. Third, despite the recitation of IgE as one of many potential antigens in the laundry list of potential antigens for antibodies [paragraph. 39], none of the specifically described antibody formulations of the '417 disclosure relate to anti-IgE antibodies. While each of these are examples of non-enabling disclosures when considered individually, considered in combination, the present invention is a compelling example of a species selection of components over a disclosure of multiple generic ranges.

First, Applicants have specifically selected arginine hydrochloride as an excipient particularly suitable for the practice of the present invention. This amounts to a species selection over the generic '417 disclosure. The antibody formulations of low turbidity and low viscosity of the claimed invention are not obtainable through simple extrapolation of the excipients of the '417 disclosure. For example, Examples 2-4, 6, 7, and 9 of '417 describe the use of succinate buffer in the antibody formulations, while Table 1 on page 75 shows that the use of succinate buffer in the formulation of the present invention results in gel formation. Examples 5 and 8 are not suitable because NaCl alone does not achieve a formulation having acceptable viscosity, turbidity and osmolarity. Applicant's selection of arginine-HCl is based not solely on its property as a tonicity modifying agent, but also on its unexpected properties as a multifunctional agent that can lower the viscosity and maintain the stability of the formulation. As a result, neither arginine alone, nor especially arginine-HCl are described with sufficient specificity in the '417 disclosure to enable the practice of the claimed invention.

Second, Applicants claims relate to anti-IgE formulations of 120 mg/ml or greater. Despite the text words of "100 mg/ml **or greater**" of antibody concentration, the '417 disclosure

only specifically describes antibody formulations having a maximum final concentration of 100 mg/ml. This is significant because the '417 disclosure does not recognize the problem of increasing viscosity. As shown previously, above 100 mg/ml, the antigen specificity of antibodies has a significant impact on the viscosity of the antibody formulation. This property is unexpected because it is not observed at lower antibody concentrations. Thus, the stable antibody formations of low turbidity and viscosity of the claimed invention are not obtainable through extrapolation of the excipients of the '417 disclosure. As a result, it is not the case that the '417 disclosure is "sufficiently specific" to enable the practice of the present invention.

Third, the antibodies of the present invention are specific for IgE. The '417 disclosure does not specifically describe the application of its antibody formulations to anti-IgE antibodies. As shown by Liu *et al., J. Pharmaceutical Sci.* 94(9): 1928 (2005) [provided in the attached Form 1449], antigen specificity, such as that resulting from changes to the variable binding region (p. 1929, Figure 8B, page 1937) have significantly different viscosities at elevated (> 100 mg/ml) concentrations with equivalent excipient levels. Thus, excipient conditions operable for antibodies specific to one antigen are not necessarily "sufficiently specific" for those of another antibody.

In summary, the prior art is not enabling because there is no disclosure or recognition of the problem of viscosity at higher protein concentrations that occurs at elevated concentrations of anti-IgE antibody. As taught by Applicants (page 2, lines 3-5) viscosity can be a particular problem when final antibody concentrations of 100 mg/ml are formulated. This problem is unexpected because it only appears at higher concentrations, and is an especially acute problem with anti-IgE antibodies. Solving the problem of higher viscosity was accomplished not with the selection of any generically known "tonicity modifier," but with the specific selection of arginine-HCl as a particularly suitable multifunctional excipient. The '417 does not recognize the unique properties of arginine as a particularly suitable excipient for lowering the viscosity of high concentration anti-IgE antibody formulations. Since the problems that are addressed by this

excipient are unexpected, the selection of it for use with the present invention is also unexpected, and a result, patentable.

Applicants request reconsideration and withdrawal of the rejection of Claims 1-15 and 20 under 35 U.S.C. § 102(e) as being anticipated by US2003/0138417 (" '417").

The Rejection under 35 U.S.C. § 103(a) as being unpatentable over US2003/0138417 in view of USP 5,994,511.

Claims 1-17, 20 and 22-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US2003/0138417 (" '417") in view of U.S. Pat. No. 5,994,511 (" '511"). Specifically, the Examiner asserts that the '511 patent teaches rhuMAbE25 composition (Table 1, claims 9-10) and an article of manufacture comprising syringes or injection tools (col. 58-59).

In response, while '417 has been described previously, Applicants agree that '511 discloses generally articles of manufacture including syringes or injection tools comprising compositions of rhuMAbE25. However, '511 does not describe the liquid formulations of the claimed invention.

Applicants have previously distinguished the key claim elements of the present invention from '417. These arguments, especially those directed to the unexpected properties of formulations of anti-IgE antibody formulations of high concentrations (> 120 mg/ml), are also applicable for consideration here in rebutting the obviousness rejection.

Under 35 U.S.C. § 103(a), the key determination is not whether the differences themselves would have been obvious, but rather, whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 218 USPQ 871 (Fed. Cir. 1983). Moreover, a particular parameter must first be recognized as a result-effective variable, that is, a variable that achieves a recognized result, before the determination of the optimum or workable ranges of said variable can be characterized as routine experimentation. M.P.E.P. § 2144.05 II (B); *In re Antonie*, 195 USPQ 6 (CCPA 1977).

In *Antonie*, the CCPA rejected the Board's confirmation of a rejection for obviousness for a wastewater treatment device claiming a ratio of tank volume to contractor area of 0.12 gal./ft^2 in order to maximize cleaning efficiency, over a prior art disclosure of a similar tank which did not recite any appreciation such a ratio being critical to cleaning efficiency. The prior art also disclosed that cleaning efficiency could be enhanced by increasing the contactor area while keeping water flow contact. From this, the Examiner extrapolated that the reference also taught the increase of contactor area while keeping the total volume contact. Continuing, the notion of increasing tank volume to surface area in order to increase efficiency was taught by the reference, and that working out the value for optimum efficiency was mere mechanical experimentation.

In reversing the Board, the Court noted that that "the invention as a whole" required not only the literal recitation of the claims (*i.e.*, the ratio value), along with its "inherent and disclosed properties." *Antoine* at 8. The Court noted with particularity that such "inherent and disclosed properties" was that devices with the disclosed ratio would have maximal cleaning efficiency, regardless of the values of the other variables.

In the case at hand, neither '417 nor '511 even recognizes the problem of increased viscosity of high concentration antibody formulations, much less that the selection of arginine-HCl is most suitable for reducing the viscosity. Thus, it is the presence of Ar-HCl, and specifically, its inherent properties of viscosity reduction, that satisfies the present invention. Just as the lack of recognition of the importance of the claimed ration in *Antoine* negated the finding of obviousness, so should the failure to recognize the viscosity reducing properties of Ar-HCl negate the finding of obviousness in the present case. In other words, the viscosity reduction property of Ar-HCl is an unexpected advantage.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1-17, 20 and 22-25 under 35 U.S.C. § 103(a) over US2003/0138417 (" '417") in view of U.S. Pat. No. 5,994,511 (" '511").

SUMMARY

Claims 1, 3-8, 16-25 and 28-45 and 48-50 are pending in the application.

If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and no fees are believed due for timely consideration. In the unlikely event that fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
GENENTECH, INC.

Date: **September 21, 2005**

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